heterocyclyl, etc.; with provisos], were prepd. Thus, 6-(4-butylaminosulfonylphenylamino)-2-chloro-9-ethyl-9H-purine, diglyme and cis-2-aminocyclohexanecarboxamide were heated at 160.degree. in a sealed tube to give 32% cis-2-[6-(4-butylaminosulfonylphenylamino)-9-ethyl-9H-purin-2-yl-amino]cyclohexanecarboxylic acid amide. I at 0.001-10 .mu.M inhibited protein tyrosine kinase pp60c-src.

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 154.06 | 582.32 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -1.77 | -31.92 |

FILE 'CAOLD' ENTERED AT 11:26:23 ON 01 FEB 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGistRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

L4 0 L3

=> del his y

=> fil reg

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 4.73 | 428.26 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -0.62 | -30.15 |

FILE 'REGISTRY' ENTERED AT 11:21:08 ON 01 FEB 2002
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Searched by: Mary Hale 308-4258 CM-1 12D16

Bech 927328

STRUCTURE FILE UPDATES: 30 JAN 2002 HIGHEST RN 388563-50-6
DICTIONARY FILE UPDATES: 30 JAN 2002 HIGHEST RN 388563-50-6

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator between 12/27/01 and 1/23/02, are encouraged to re-run these strategies. Contact the CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698, worldwide, or send an e-mail to help@cas.org for further assistance or to receive a credit for any duplicate searches.

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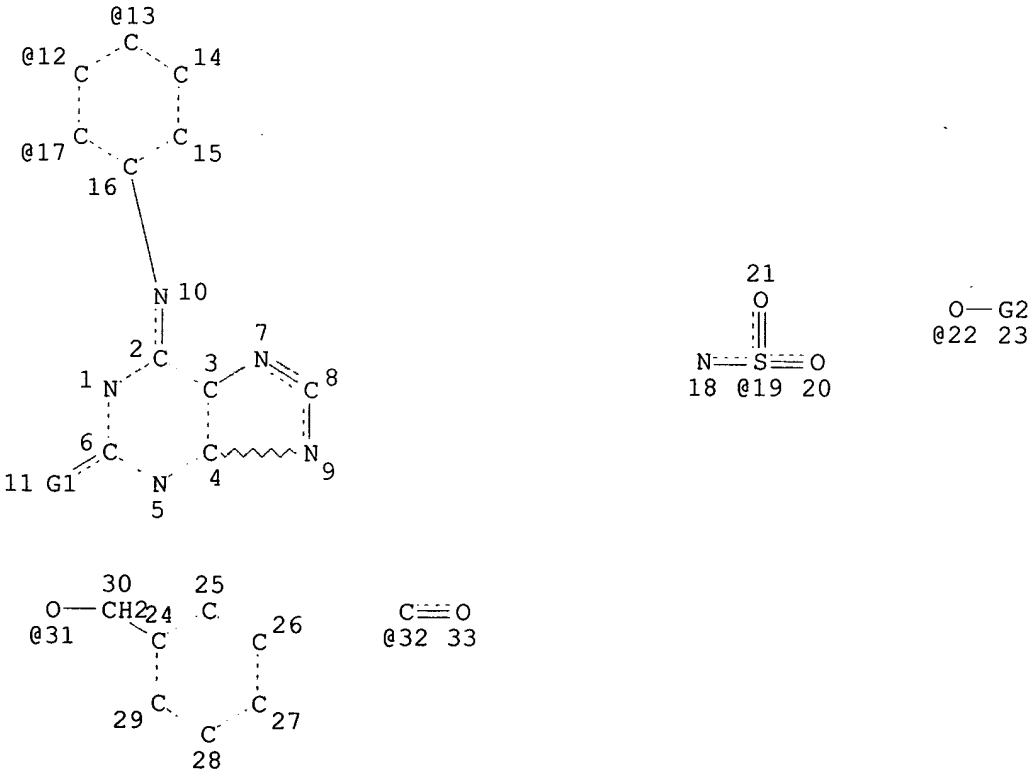
L1 STR




Searched by: Mary Hale 308-4258 CM-1 12D16

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VAR G2=32/S/P
VPA 19-17/12/13 U
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE
L3 3 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 6 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.02

L3 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 310401-80-0 REGISTRY
CN Benzenesulfonamide, 4-[(2-chloro-9-cyclopentyl-9H-purin-6-yl)amino]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
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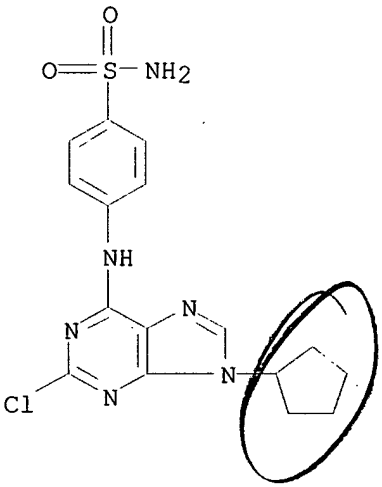
SR CA
LC STN Files: CA, CAPLUS



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:17347 Preparation and formulation of purine derivatives for a variety of pharmaceutical uses. Haesslein, Jean-Luc (Hoechst Marion Roussel, Fr.). PCT Int. Appl. WO 2000071543 A1 20001130, 203 pp. DESIGNATED STATES: W: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC,

Searched by: Mary Hale 308-4258 CM-1 12D16

ML, MR, NE, NL, PT, SE, SN, TD, TG. (French). CODEN: PIXXD2.
APPLICATION: WO 2000-FR1335 20000518. PRIORITY: FR 1999-6456 19990521.

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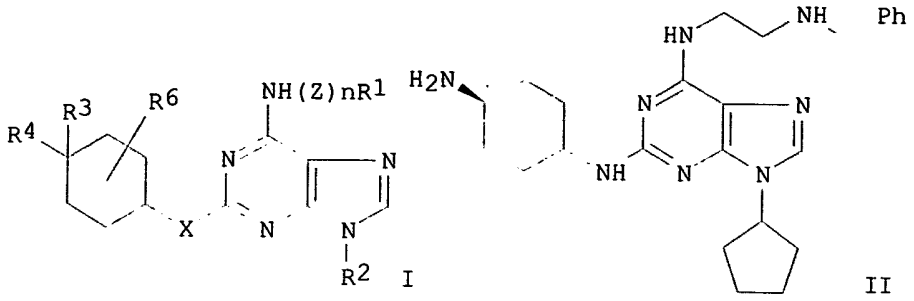
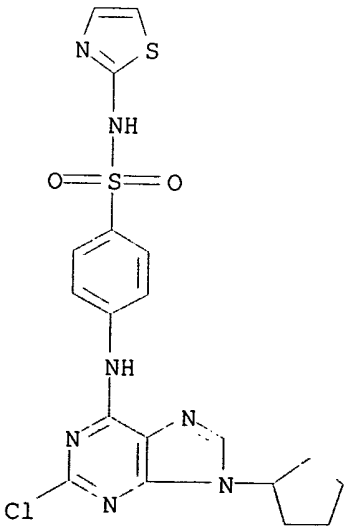



AB Purines, such as I [R1 = H, aryl, alkyl, sulfonyl, heterocyclyl; R2 = alkyl, cycloalkyl, heterocyclyl; R3, R4 = H, OH, NH2, alkyl, alkoxy, alkylamino, arylamino, etc.; R3R4 = O, oxime; R6 = H, OH, halogen, alkyl, alkoxy, etc; Y = O, NR5; R5 = H, CO2CMe3, alkyl, cycloalkyl; Z = NH, CH2, SO2, CO, COO, CONH, etc.; n = 1, 2], were prepd. for pharmaceutical use in the treatment of diseases, such as cancer, psoriasis, parasitoses, Alzheimer's, and neurodegeneration (no biol. testing data presented). Thus, purine II was prepd. starting from 2,6-dichloropurine, cyclopentanol, trans-1,4-cyclohexanediamine, 1,2-ethanediamine, and benzaldehyde. Also, pharmaceutical formulations of the prepd. purines were presented.

L3 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 310401-79-7 REGISTRY
CN Benzenesulfonamide, 4-[(2-chloro-9-cyclopentyl-9H-purin-6-yl)amino]-N-2-thiazolyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C19 H18 Cl N7 O2 S2
SR CA
LC STN Files: CA, CAPLUS




Searched by: Mary Hale 308-4258 CM-1 12D16

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:17347 Preparation and formulation of purine derivatives for a variety of pharmaceutical uses. Haesslein, Jean-Luc (Hoechst Marion Roussel, Fr.). PCT Int. Appl. WO 2000071543 A1 20001130, 203 pp. DESIGNATED STATES: W: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (French). CODEN: PIXXD2. APPLICATION: WO 2000-FR1335 20000518. PRIORITY: FR 1999-6456 19990521.

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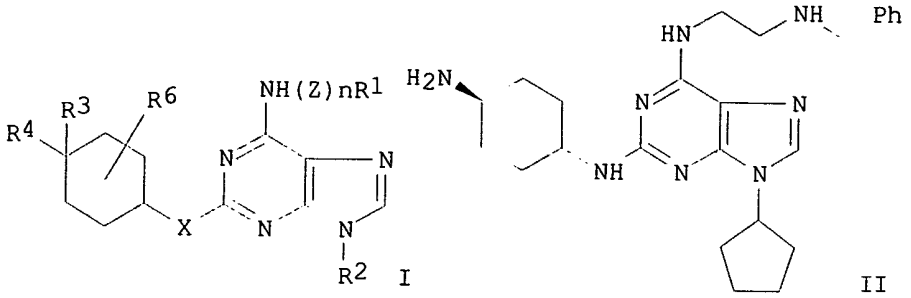
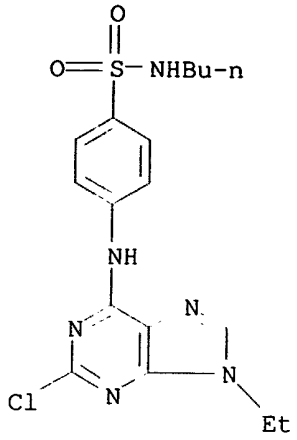



AB Purines, such as I [R1 = H, aryl, alkyl, sulfonyl, heterocyclyl; R2 = alkyl, cycloalkyl, heterocyclyl; R3, R4 = H, OH, NH2, alkyl, alkoxy, alkylamino, arylamino, etc.; R3R4 = O, oxime; R6 = H, OH, halogen, alkyl, alkoxy, etc; Y = O, NR5; R5 = H, CO2CMe3, alkyl, cycloalkyl; Z = NH, CH2, SO2, CO, COO, CONH, etc.; n = 1, 2], were prepd. for pharmaceutical use in the treatment of diseases, such as cancer, psoriasis, parasitoses, Alzheimer's, and neurodegeneration (no biol. testing data presented). Thus, purine II was prepd. starting from 2,6-dichloropurine, cyclopentanol, trans-1,4-cyclohexanediamine, 1,2-ethanediamine, and benzaldehyde. Also, pharmaceutical formulations of the prepd. purines were presented.

L3 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 289480-15-5 REGISTRY
CN Benzenesulfonamide, N-butyl-4-[(2-chloro-9-ethyl-9H-purin-6-yl)amino]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C17 H21 Cl N6 O2 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Searched by: Mary Hale 308-4258 CM-1 12D16



Thank you

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:193164 Preparation of 2-amino-6-anilinopurines as inhibitors of p34cdc2/cyclin Bcdc13 kinase and protein tyrosine kinase pp60c-src.. Imbach, Patricia; Capraro, Hans-Georg; Zimmermann, Jurg; Caravatti, Giorgio; Furet, Pascal; Brill, Wolfgang Karl-Diether (Novartis A.-G., Switz.; Novartis-Erfindungen). PCT Int. Appl. WO 2000049018 A1 20000824, 100 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP1271 20000216. PRIORITY: GB 1999-3762 19990218.

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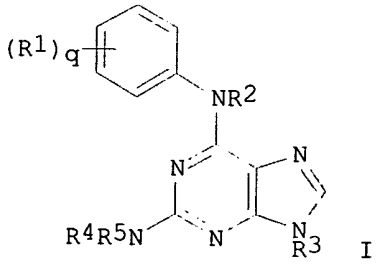


I

AB Title compds. [I; q = 1-5; R1 = SONR6R7, SO2NR6R7, aralkylcarbamoyl, etc.; R2 = H, carbamoyl, alkylcarbamoyl; R3 = (substituted) aliphatyl; R5 amino, OH, PhO, alkoxy, acyl, substituted aliphatyl, carbocyclyl, heterocyclyl, etc.; R4 = H, R5; R4R5, R6R7 = (substituted) alkylene, alkenylene optionally interrupted by O, S, N; R6, R7 = H, aliphatyl, carbocyclyl,

Searched by: Mary Hale 308-4258 CM-1 12D16

| | ENTRY | SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.32 | 254.75 |

1927322

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | 0.00 | -25.40 |

FILE 'REGISTRY' ENTERED AT 11:16:13 ON 01 FEB 2002


STRUCTURE FILE UPDATES: 30 JAN 2002 HIGHEST RN 388563-50-6

Searched by: Mary Hale 308-4258 CM-1 12D16

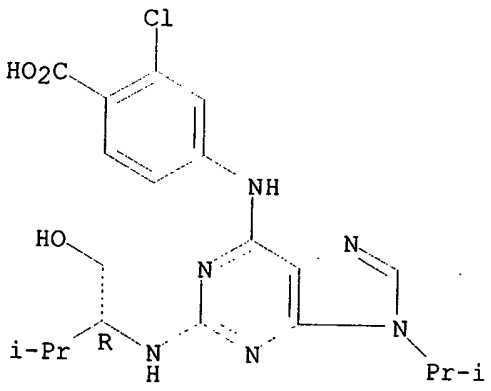
site of the human cyclin-dependent kinase 2 (CDK2). By iterating chem. library synthesis and biol. screening, potent inhibitors of the human CDK2-cyclin A kinase complex and of Saccharomyces cerevisiae Cdc28p were identified. The structural basis for the binding affinity and selectivity was detd. by anal. of a three-dimensional crystal structure of a CDK2-inhibitor complex. The cellular effects of these compds. were characterized in mammalian cells and yeast. In the latter case the effects were characterized on a genome-wide scale by monitoring changes in mRNA levels in treated cells with high-d. oligonucleotide probe arrays. Purine libraries could provide useful tools for analyzing a variety of signaling and regulatory pathways and may led to the development of new therapeutics.

IT **212844-54-7D**, complexes with CDK2 protein kinase
RL: PRP (Properties)
(crystal structure; prepn. and characterization of a combinatorial library of 2,6,9-trisubstituted purine inhibitors of protein kinases)

RN 212844-54-7 CAPLUS

CN Benzoic acid, 2-chloro-4-[[2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.




RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(prepn. and characterization of a combinatorial library of 2,6,9-trisubstituted purine inhibitors of protein kinases

=> del his y

DICTIONARY FILE UPDATES: 30 JAN 2002 HIGHEST RN 388563-50-6

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator between 12/27/01 and 1/23/02, are encouraged to re-run these strategies. Contact the CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698, worldwide, or send an e-mail to help@cas.org for further assistance or to receive a credit for any duplicate searches.

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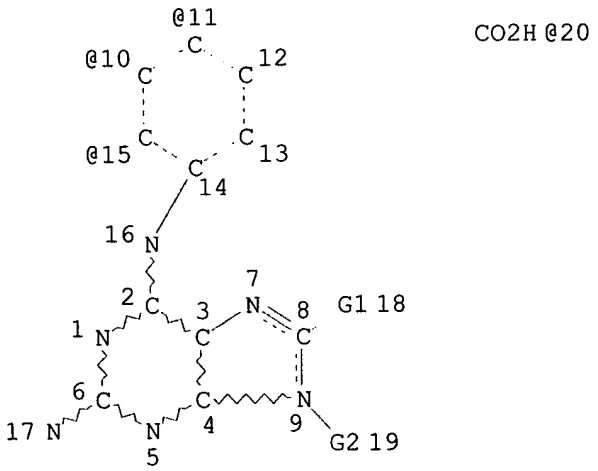


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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

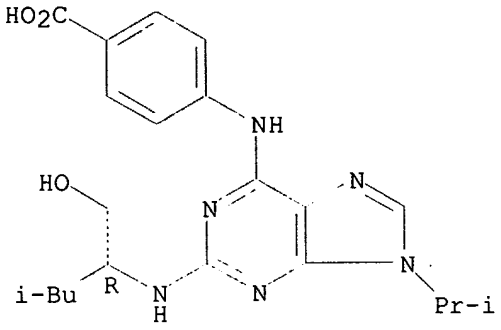
Searched by: Mary Hale 308-4258 CM-1 12D16

STEREO ATTRIBUTES: NONE
L5 7 SEA FILE=REGISTRY SSS FUL L3

100.0% PROCESSED 121 ITERATIONS 7 ANSWERS
SEARCH TIME: 00.00.01

L5 ANSWER 1 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 361431-83-6 REGISTRY
CN Benzoic acid, 4-[[2-[[(1R)-1-(hydroxymethyl)-3-methylbutyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H28 N6 O3
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

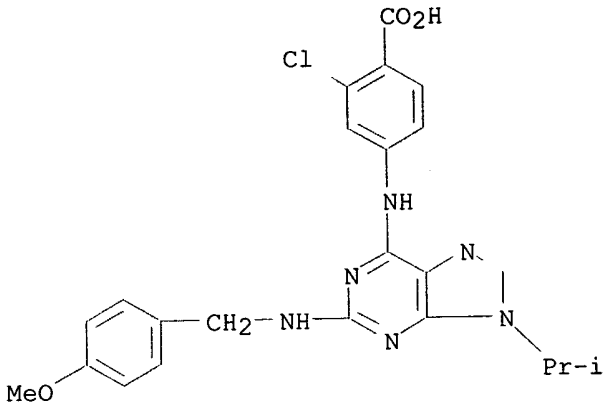
REFERENCE 1: 135:251928 Discovery of estrogen sulfotransferase inhibitors from a purine library screen. Verdugo, Dawn E.; Cancilla, Mark T.; Ge, Xue; Gray, Nathanael S.; Chang, Young-Tae; Schultz, Peter G.; Negishi, Masahiko; Leary, Julie A.; Bertozzi, Carolyn R. (Departments of Chemistry and Molecular and Cell Biology, University of California, Berkeley, CA, 94720, USA). Journal of Medicinal Chemistry, 44(17), 2683-2686 (English) 2001. CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.

AB There is now substantial evidence that sulfated biomols. (i.e., carbohydrates, proteins, and steroids) contribute to many disease states, including chronic inflammation, HIV-1 infection, and hormone-dependent breast tumor growth. The sulfate ester is often a key determinant of bioactivity, directing significant attention to the corresponding enzymes, the sulfotransferases, as a new class of therapeutic targets. Estrogen sulfotransferase (EST) catalyzes the transfer of a sulfuryl group from 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to estrogen (3,17-.beta.-estradiol) and estrogen-like compds. in the cytosol, solubilizing them to maintain hormone homeostasis. Herein we report the discovery of potent and selective EST inhibitors derived from a purine-based library that possess all of the qualities required for cell-based and pharmacol. studies. In addn., we report the application of

Searched by: Mary Hale 308-4258 CM-1 12D16

a recently described mass spectrometry (MS) assay for rapid identification of novel inhibitors for this therapeutically interesting sulfotransferase. Members of this purine-based library have the benefit of drug-like properties. We have discovered several purine- based inhibitors, including one with nanomolar potency, for EST using two parallel screening methods. The most potent of these compds. may prove useful as chem. tools for elucidating the role of EST in steroid homeostasis and tumor cell proliferation.

L5 ANSWER 2 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 361431-23-4 REGISTRY
CN Benzoic acid, 2-chloro-4-[[2-[[(4-methoxyphenyl)methyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C23 H23 Cl N6 O3
SR CA
LC STN Files: CA, CAPLUS, TOXLIT




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

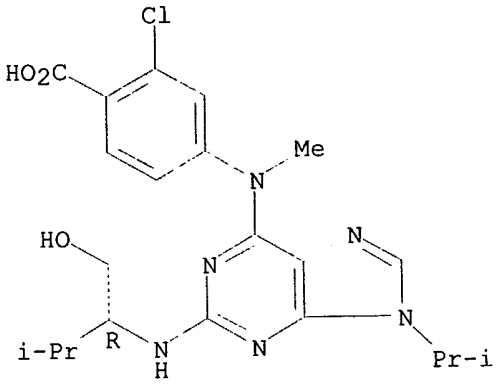
REFERENCE 1: 135:251928 Discovery of estrogen sulfotransferase inhibitors from a purine library screen. Verdugo, Dawn E.; Cancilla, Mark T.; Ge, Xue; Gray, Nathanael S.; Chang, Young-Tae; Schultz, Peter G.; Negishi, Masahiko; Leary, Julie A.; Bertozzi, Carolyn R. (Departments of Chemistry and Molecular and Cell Biology, University of California, Berkeley, CA, 94720, USA). Journal of Medicinal Chemistry, 44(17), 2683-2686 (English) 2001. CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.

AB There is now substantial evidence that sulfated biomols. (i.e., carbohydrates, proteins, and steroids) contribute to many disease states, including chronic inflammation, HIV-1 infection, and hormone-dependent breast tumor growth. The sulfate ester is often a key determinant of bioactivity, directing significant attention to the corresponding enzymes, the sulfotransferases, as a new class of therapeutic targets. Estrogen sulfotransferase (EST) catalyzes the transfer of a sulfuryl group from 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to estrogen (3,17-.beta.-estradiol) and estrogen-like compds. in the cytosol, solubilizing them to maintain hormone homeostasis. Herein we report the discovery of potent and selective EST inhibitors derived from a purine-based library that possess all of the qualities required for cell-based and pharmacol. studies. In addn., we report the application of

a recently described mass spectrometry (MS) assay for rapid identification of novel inhibitors for this therapeutically interesting sulfotransferase. Members of this purine-based library have the benefit of drug-like properties. We have discovered several purine- based inhibitors, including one with nanomolar potency, for EST using two parallel screening methods. The most potent of these compds. may prove useful as chem. tools for elucidating the role of EST in steroid homeostasis and tumor cell proliferation.

L5 ANSWER 3 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 289508-12-9 REGISTRY
CN Benzoic acid, 2-chloro-4-[[2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]methylamino]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Methylpurvalanol B
FS STEREOSEARCH
MF C21 H27 Cl N6 O3
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

2 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:282675 Structure-activity relationships and inhibitory effects of various purine derivatives on the in vitro growth of Plasmodium falciparum. Harmse, L.; van Zyl, R.; Gray, N.; Schultz, P.; Leclerc, S.; Meijer, L.; Doerig, C.; Havlik, I. (Faculty of Health Sciences, Department of Experimental and Clinical Pharmacology, University of the Witwatersrand, Parktown, 2193, S. Afr.). Biochemical Pharmacology, 62(3), 341-348 (English) 2001. CODEN: BCPCA6. ISSN: 0006-2952. Publisher: Elsevier Science Inc..
AB The development of novel chemotherapeutic agents has become an urgent task due to the development and rapid spread of drug resistance in Plasmodium falciparum, the protozoan parasite responsible for cerebral malaria. Cyclin-dependent kinases (CDKs) are essential for the regulation of the eukaryotic cell cycle, and several enzymes of this family have been identified in P. falciparum. In recent years, a no. of purine-derived kinase inhibitors have been synthesized, some of which display selective activity against CDKs. This report describes a study in which various

purine derivs. were screened for in vitro antimalarial activity. The erythrocytic asexual stages of the chloroquine-resistant P. falciparum strain (FCR-3) were cultivated in vitro in the presence of the various purines, and their effect on parasite proliferation was detd. by the [3H]hypoxanthine incorporation assay. Our results show considerable variation in the sensitivity of P. falciparum to the different purines, as well as a general independence from their effect on purified starfish CDK1/cyclin B activity, which has been the std. assay used to identify CDK-specific inhibitors. Two subfamilies of purines with moderate to poor activity against CDK1/cyclin B activity showed submicromolar activity against P. falciparum. Structure-activity anal. indicates that certain structural features are assocd. with increased activity against P. falciparum. These features can be exploited to synthesize compds. with higher activity and specificity towards P. falciparum.

REFERENCE 2: 133:187904 Intracellular targets of cyclin-dependent kinase inhibitors: identification by affinity chromatography using immobilised inhibitors. Knockaert, M.; Gray, N.; Damiens, E.; Chang, Y-T.; Grellier, P.; Grant, K.; Fergusson, D.; Mottram, J.; Soete, M.; Dubremetz, J-F.; Le Roch, K.; Doerig, C.; Schultz, P. G.; Meijer, L. (Station Biologique de Roscoff, CNRS, Roscoff, 29682, Fr.). Chem. Biol., 7(6), 411-422 (English) 2000. CODEN: CBOLE2. ISSN: 1074-5521. Publisher: Elsevier Science Ltd..

AB Background: Chem. inhibitors of cyclin-dependent kinases (CDKs) have great therapeutic potential against various proliferative and neurodegenerative disorders. Olomoucine, a 2,6,9-trisubstituted purine, has been optimized for activity against CDK1/cyclin B by combinatorial and medicinal chem. efforts to yield the purvalanol inhibitors. Although many studies support the action of purvalanols against CDKs, the actual intracellular targets of 2,6,9-trisubstituted purines remain unverified. Results: To address this issue, purvalanol B (I) and an N6-methylated, CDK-inactive deriv. were immobilized on an agarose matrix. Exts. from a diverse collection of cell types and organisms were screened for proteins binding purvalanol B. In addn. to validating CDKs as intracellular targets, a variety of unexpected protein kinases were recovered from the I matrix. Casein kinase 1 (CK1) was identified as a principal I matrix binding protein in Plasmodium falciparum, Leishmania mexicana, Toxoplasma gondii and trypanosoma cruzi. Purvalanol compds. also inhibit the proliferation of these parasites, suggesting that CK1 is a valuable target for further screening with 2,6,9-trisubstituted purine libraries. Conclusions: That a simple batchwise affinity chromatog. approach using two purine derivs. facilitated isolation of a small set of highly purified kinases suggests that this could be a general method for identifying intracellular targets relevant to a particular class of ligands. This method allows a close correlation to be established between the pattern of proteins bound to a small family of related compds. and the pattern of cellular responses to these compds.

L5 ANSWER 4 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 289480-16-6 REGISTRY
CN Benzoic acid, 4-[[9-ethyl-2-[(trans-4-hydroxycyclohexyl)amino]-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
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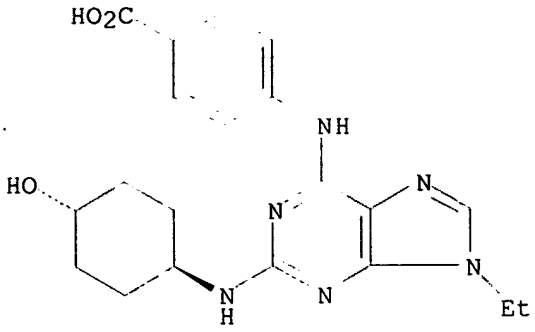
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Relative stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:193164 Preparation of 2-amino-6-anilinopurines as inhibitors of p34cdc2/cyclin Bcdc13 kinase and protein tyrosine kinase pp60c-src.. Imbach, Patricia; Capraro, Hans-Georg; Zimmermann, Jurg; Caravatti, Giorgio; Furet, Pascal; Brill, Wolfgang Karl-Diether (Novartis A.-G., Switz.; Novartis-Erfindungen). PCT Int. Appl. WO 2000049018 A1 20000824, 100 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP1271 20000216. PRIORITY: GB 1999-3762 19990218.

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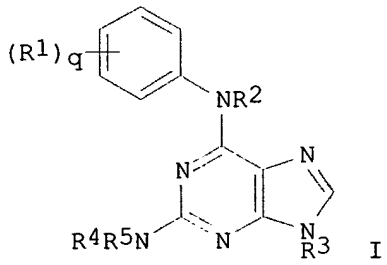

I

AB Title compds. [I; q = 1-5; R1 = SONR6R7, SO2NR6R7, aralkylcarbamoyl, etc.; R2 = H, carbamoyl, alkylcarbamoyl; R3 = (substituted) aliphatyl; R5 amino, OH, PhO, alkoxy, acyl, substituted aliphatyl, carbocyclyl, heterocyclyl, etc.; R4 = H, R5; R4R5, R6R7 = (substituted) alkylene, alkenylene optionally interrupted by O, S, N; R6, R7 = H, aliphatyl, carbocyclyl, heterocyclyl, etc.; with provisos], were prepd. Thus, 6-(4-butylaminosulfonylphenylamino)-2-chloro-9-ethyl-9H-purine, diglyme and cis-2-aminocyclohexanecarboxamide were heated at 160.degree. in a sealed tube to give 32% cis-2-[6-(4-butylaminosulfonylphenylamino)-9-ethyl-9H-purin-2-yl-amino]cyclohexanecarboxylic acid amide. I at 0.001-10 .mu.M inhibited protein tyrosine kinase pp60c-src.

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L5 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 220792-62-1 REGISTRY
CN Benzoic acid, 2-hydroxy-5-[[2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)
OTHER NAMES:
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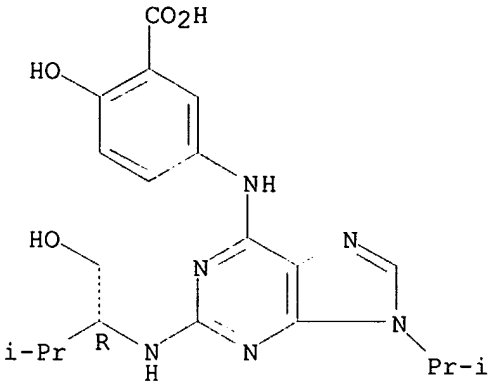
LC STN Files: CA, CAPLUS, TOXCENTER, TOXLIT, USPATFULL

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:251928 Discovery of estrogen sulfotransferase inhibitors from a purine library screen. Verdugo, Dawn E.; Cancilla, Mark T.; Ge, Xue; Gray, Nathanael S.; Chang, Young-Tae; Schultz, Peter G.; Negishi, Masahiko; Leary, Julie A.; Bertozzi, Carolyn R. (Departments of Chemistry and Molecular and Cell Biology, University of California, Berkeley, CA, 94720, USA). Journal of Medicinal Chemistry, 44(17), 2683-2686 (English) 2001. CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.

AB There is now substantial evidence that sulfated biomols. (i.e., carbohydrates, proteins, and steroids) contribute to many disease states, including chronic inflammation, HIV-1 infection, and hormone-dependent breast tumor growth. The sulfate ester is often a key determinant of bioactivity, directing significant attention to the corresponding enzymes, the sulfotransferases, as a new class of therapeutic targets. Estrogen sulfotransferase (EST) catalyzes the transfer of a sulfuryl group from 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to estrogen (3,17-.beta.-estradiol) and estrogen-like compds. in the cytosol, solubilizing them to maintain hormone homeostasis. Herein we report the discovery of potent and selective EST inhibitors derived from a purine-based library that possess all of the qualities required for cell-based and pharmacol. studies. In addn., we report the application of a recently described mass spectrometry (MS) assay for rapid identification of novel inhibitors for this therapeutically interesting sulfotransferase. Members of this purine-based library have the benefit of drug-like properties. We have discovered several purine- based inhibitors,

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including one with nanomolar potency, for EST using two parallel screening methods. The most potent of these compds. may prove useful as chem. tools for elucidating the role of EST in steroid homeostasis and tumor cell proliferation.

REFERENCE 2: 131:228582 Synthesis and application of functionally diverse 2,6,9-trisubstituted purine libraries as CDK inhibitors. Chang, Young-Tae; Gray, Nathanael S.; Rosania, Gustavo R.; Sutherlin, Daniel P.; Kwon, Soojin; Norman, Thea C.; Sarohia, Radhika; Leost, Maryse; Meijer, Laurent; Schultz, Peter G. (Lawrence Berkeley National Laboratory and the Howard Hughes Medical Institute, Department of Chemistry, University of California, Berkeley, CA, 94720, USA). Chem. Biol., 6(6), 361-375 (English) 1999. CODEN: CBOLE2. ISSN: 1074-5521. Publisher: Current Biology Publications.

AB Purines constitute a structural class of protein ligands involved in mediating an astonishing array of metabolic processes and signal pathways in all living organisms. Synthesis of purine derivs. targeting specific purine-binding proteins in vivo could lead to versatile lead compds. for use as biol. probes or drug candidates. We synthesized several libraries of 2,6,9-trisubstituted purines using both soln.- and solid-phase chem., and screened the compds. for inhibition of cyclin-dependent kinase (CDK) activity and human leukemic cell growth. Lead compds. were optimized by iterative synthesis based on structure-activity relationships (SARs), as well as anal. of several CDK-inhibitor cocrystal structures, to afford several interesting compds. including one of the most potent CDK inhibitors known to date. Unexpectedly, some compds. with similar CDK inhibitory activity arrested cellular proliferation at distinctly different phases of the cell cycle, and another inhibitor directly induced apoptosis, bypassing cell-cycle arrest. Some of these compds. selectively inhibited growth of cells derived from specific tumors. 2,6,9-Trisubstituted purines have various and potent biol. activities, despite high concns. of competing endogenous purine ligands in living cells. Purine libraries constitute a versatile source of small mols. that affect distinct biochem. pathways mediating different cellular functions.

REFERENCE 3: 131:82944 Methods of using chemical libraries to search for new kinase inhibitors. Gray, Nathanael S.; Schultz, Peter; Wodicka, Lisa; Meijer, Laurent; Lockhart, David J. (The Regents of the University of California, USA; Affymetrix; Centre National de la Recherche Scientifique). PCT Int. Appl. WO 9934018 A1 19990708, 103 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US27405 19981223. PRIORITY: US 1997-68798 19971224.

AB The generation of selective inhibitors for specific protein kinases would provide new tools for analyzing signal transduction pathways and possibly new therapeutic agents. We have invented an approach to the development of selective protein kinase inhibitors based on the unexpected binding mode of 2,6,9-trisubstituted purines to the ATP binding site of human CDK2. The most potent inhibitor, purvalanol B (IC50 = 6 nM), binds with a 30-fold greater affinity than the known CDK2 inhibitor, flavopiridol. The cellular effects of this class of compds. were examd. and compared to those of flavopiridol by monitoring changes in mRNA expression levels for all genes in treated cells of Saccharomyces cerevisiae using high-d. oligonucleotide probe arrays.

REFERENCE 4: 130:196532 Preparation of purine derivatives as inhibitor of protein kinases, G-proteins and polymerases. Gray, Nathanael S.; Schultz,

Peter; Kim, Sung-Hou; Meijer, Laurent (The Regents of the University of California, USA). PCT Int. Appl. WO 9907705 A1 19990218, 67 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US16388 19980806. PRIORITY: US 1997-55400 19970807.

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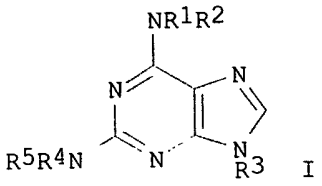


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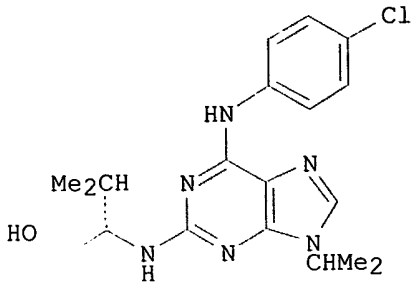


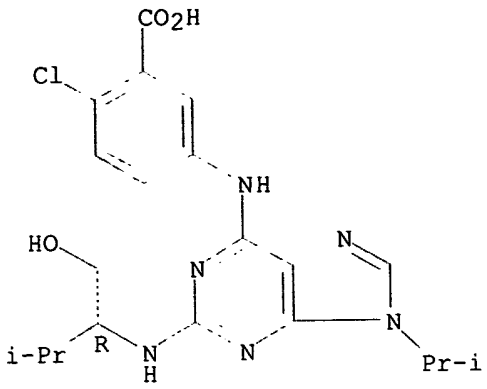

II

AB The purine analogs I (R1, R2, R3, R4, R5 are independently members selected from the group consisting of H, C1-C8 straight-chain, branched-chain, satd. and unsatd. alkyl, C1-C8 straight-chain, branched-chain, satd. and unsatd. substituted alkyl, aryl and substituted aryl) or a pharmaceutically acceptable salt thereof were prepd. for inhibition of inter alia, protein kinases, G-proteins and polymerases. In addn., the present invention relates to methods of using such purine analogs to inhibit protein kinases, G-proteins, polymerases and other cellular processes and to treat cellular proliferative diseases. Thus, 2-fluoro-6-chloropurine was alkylated with 2-propanol followed by amination with 3-chloroaniline and then S-2-amino-3-methyl-1-butanol to give the purine II.

L5 ANSWER 6 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 220792-55-2 REGISTRY
CN Benzoic acid, 2-chloro-5-[[2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN NG 96
FS STEREOSEARCH
MF C20 H25 Cl N6 O3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, TOXLIT, USPATFULL

Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

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4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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AB There is now substantial evidence that sulfated biomols. (i.e., carbohydrates, proteins, and steroids) contribute to many disease states, including chronic inflammation, HIV-1 infection, and hormone-dependent breast tumor growth. The sulfate ester is often a key determinant of bioactivity, directing significant attention to the corresponding enzymes, the sulfotransferases, as a new class of therapeutic targets. Estrogen sulfotransferase (EST) catalyzes the transfer of a sulfuryl group from 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to estrogen (3,17-.beta.-estradiol) and estrogen-like compds. in the cytosol, solubilizing them to maintain hormone homeostasis. Herein we report the discovery of potent and selective EST inhibitors derived from a purine-based library that possess all of the qualities required for cell-based and pharmacol. studies. In addn., we report the application of a recently described mass spectrometry (MS) assay for rapid identification of novel inhibitors for this therapeutically interesting sulfotransferase. Members of this purine-based library have the benefit of drug-like properties. We have discovered several purine- based inhibitors, including one with nanomolar potency, for EST using two parallel screening methods. The most potent of these compds. may prove useful as chem. tools for elucidating the role of EST in steroid homeostasis and tumor cell proliferation.

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AB Purines constitute a structural class of protein ligands involved in mediating an astonishing array of metabolic processes and signal pathways in all living organisms. Synthesis of purine derivs. targeting specific purine-binding proteins in vivo could lead to versatile lead compds. for use as biol. probes or drug candidates. We synthesized several libraries of 2,6,9-trisubstituted purines using both soln.- and solid-phase chem., and screened the compds. for inhibition of cyclin-dependent kinase (CDK) activity and human leukemic cell growth. Lead compds. were optimized by iterative synthesis based on structure-activity relationships (SARs), as well as anal. of several CDK-inhibitor cocrystal structures, to afford several interesting compds. including one of the most potent CDK inhibitors known to date. Unexpectedly, some compds. with similar CDK inhibitory activity arrested cellular proliferation at distinctly different phases of the cell cycle, and another inhibitor directly induced apoptosis, bypassing cell-cycle arrest. Some of these compds. selectively inhibited growth of cells derived from specific tumors. 2,6,9-Trisubstituted purines have various and potent biol. activities, despite high concns. of competing endogenous purine ligands in living cells. Purine libraries constitute a versatile source of small mols. that affect distinct biochem. pathways mediating different cellular functions.

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AB The generation of selective inhibitors for specific protein kinases would provide new tools for analyzing signal transduction pathways and possibly new therapeutic agents. We have invented an approach to the development of selective protein kinase inhibitors based on the unexpected binding mode of 2,6,9-trisubstituted purines to the ATP binding site of human CDK2. The most potent inhibitor, purvalanol B (IC50 = 6 nM), binds with a 30-fold greater affinity than the known CDK2 inhibitor, flavopiridol. The cellular effects of this class of compds. were examd. and compared to those of flavopiridol by monitoring changes in mRNA expression levels for all genes in treated cells of Saccharomyces cerevisiae using high-d. oligonucleotide probe arrays.

REFERENCE 4: 130:196532 Preparation of purine derivatives as inhibitor of protein kinases, G-proteins and polymerases. Gray, Nathanael S.; Schultz, Peter; Kim, Sung-Hou; Meijer, Laurent (The Regents of the University of California, USA). PCT Int. Appl. WO 9907705 A1 19990218, 67 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US16388 19980806. PRIORITY: US 1997-55400 19970807.

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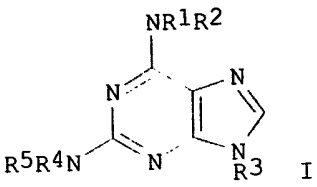

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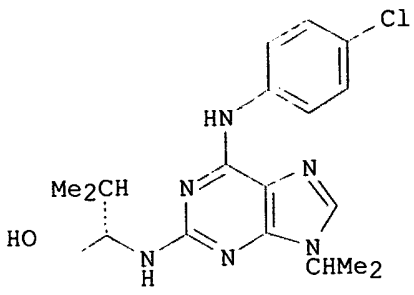
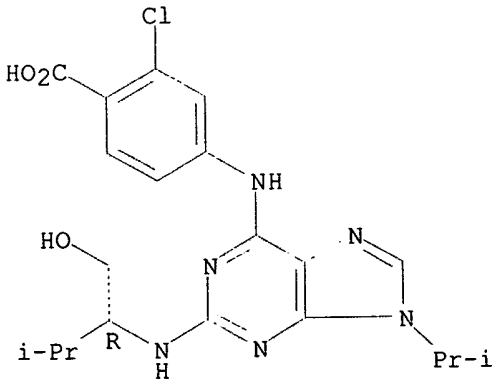


II

AB The purine analogs I (R1, R2, R3, R4, R5 are independently members selected from the group consisting of H, C1-C8 straight-chain, branched-chain, satd. and unsatd. alkyl, C1-C8 straight-chain, branched-chain, satd. and unsatd. substituted alkyl, aryl and substituted aryl) or a pharmaceutically acceptable salt thereof were prepd. for inhibition of inter alia, protein kinases, G-proteins and polymerases. In addn., the present invention relates to methods of using such purine analogs to inhibit protein kinases, G-proteins, polymerases and other cellular processes and to treat cellular proliferative diseases. Thus, 2-fluoro-6-chloropurine was alkylated with 2-propanol followed by amination with 3-chloroaniline and then S-2-amino-3-methyl-1-butanol to give the purine II.

L5 ANSWER 7 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 212844-54-7 REGISTRY
CN Benzoic acid, 2-chloro-4-[[2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN NG 95
CN Purvalanol B
FS STEREOSEARCH
MF C20 H25 Cl N6 O3
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, EMBASE, TOXCENTER, TOXLIT, USPATFULL

Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

10 REFERENCES IN FILE CA (1967 TO DATE)

Searched by: Mary Hale 308-4258 CM-1 12D16

4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
10 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:282675 Structure-activity relationships and inhibitory effects of various purine derivatives on the in vitro growth of Plasmodium falciparum. Harmse, L.; van Zyl, R.; Gray, N.; Schultz, P.; Leclerc, S.; Meijer, L.; Doerig, C.; Havlik, I. (Faculty of Health Sciences, Department of Experimental and Clinical Pharmacology, University of the Witwatersrand, Parktown, 2193, S. Afr.). Biochemical Pharmacology, 62(3), 341-348 (English) 2001. CODEN: BCPCA6. ISSN: 0006-2952. Publisher: Elsevier Science Inc..

AB The development of novel chemotherapeutic agents has become an urgent task due to the development and rapid spread of drug resistance in Plasmodium falciparum, the protozoan parasite responsible for cerebral malaria. Cyclin-dependent kinases (CDKs) are essential for the regulation of the eukaryotic cell cycle, and several enzymes of this family have been identified in P. falciparum. In recent years, a no. of purine-derived kinase inhibitors have been synthesized, some of which display selective activity against CDKs. This report describes a study in which various purine derivs. were screened for in vitro antimalarial activity. The erythrocytic asexual stages of the chloroquine-resistant P. falciparum strain (FCR-3) were cultivated in vitro in the presence of the various purines, and their effect on parasite proliferation was detd. by the [3H]hypoxanthine incorporation assay. Our results show considerable variation in the sensitivity of P. falciparum to the different purines, as well as a general independence from their effect on purified starfish CDK1/cyclin B activity, which has been the std. assay used to identify CDK-specific inhibitors. Two subfamilies of purines with moderate to poor activity against CDK1/cyclin B activity showed submicromolar activity against P. falciparum. Structure-activity anal. indicates that certain structural features are assocd. with increased activity against P. falciparum. These features can be exploited to synthesize compds. with higher activity and specificity towards P. falciparum.

REFERENCE 2: 135:251928 Discovery of estrogen sulfotransferase inhibitors from a purine library screen. Verdugo, Dawn E.; Cancilla, Mark T.; Ge, Xue; Gray, Nathanael S.; Chang, Young-Tae; Schultz, Peter G.; Negishi, Masahiko; Leary, Julie A.; Bertozzi, Carolyn R. (Departments of Chemistry and Molecular and Cell Biology, University of California, Berkeley, CA, 94720, USA). Journal of Medicinal Chemistry, 44(17), 2683-2686 (English) 2001. CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.

AB There is now substantial evidence that sulfated biomols. (i.e., carbohydrates, proteins, and steroids) contribute to many disease states, including chronic inflammation, HIV-1 infection, and hormone-dependent breast tumor growth. The sulfate ester is often a key determinant of bioactivity, directing significant attention to the corresponding enzymes, the sulfotransferases, as a new class of therapeutic targets. Estrogen sulfotransferase (EST) catalyzes the transfer of a sulfuryl group from 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to estrogen (3,17-.beta.-estradiol) and estrogen-like compds. in the cytosol, solubilizing them to maintain hormone homeostasis. Herein we report the discovery of potent and selective EST inhibitors derived from a purine-based library that possess all of the qualities required for cell-based and pharmacol. studies. In addn., we report the application of a recently described mass spectrometry (MS) assay for rapid identification of novel inhibitors for this therapeutically interesting sulfotransferase. Members of this purine-based library have the benefit of drug-like properties. We have discovered several purine- based inhibitors, including one with nanomolar potency, for EST using two parallel screening methods. The most potent of these compds. may prove useful as chem. tools for elucidating the role of EST in steroid homeostasis and tumor cell

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proliferation.

REFERENCE 3: 134:95058 CDK inhibition and the therapeutic potential of targeting the cell cycle. Lee, Chul-Hoon; Cho, Youl-Hee (Department of Medical Genetics, Hanyang University College of Medicine, Seoul, S. Korea). Hanyang Uidae Haksulchi, 20(1), 43-53 (Korean) 2000. CODEN: HIHAD3. ISSN: 0254-5942. Publisher: Hanyang University, Medical College.

AB A review with 68 refs. The cell-division cycle is a tightly controlled process that is regulated by the cyclin/CDK family of protein kinase complexes. Stringent control of this process is essential to ensure that DNA synthesis and subsequent mitotic division are accurately and coordinately executed. There is now strong evidence that CDKs, their regulators, and substrates are the targets of genetic alteration in many human cancers. As a result of this, the CDKs have been targeted for drug discovery and a no. of small mol. inhibitors of CDKs have been identified. Our attempt here is to illustrate the potential for development of therapeutics to treat human cancers by interfering with cell-cycle progression. Because of the central role that they play in advancing the division cycle, CDKs have been targeted for drug discovery and a no. of small mol. compds. have now been identified as CDK inhibitors. These strategies and other targets of intervention within the cell cycle are discussed in our review.

REFERENCE 4: 133:187904 Intracellular targets of cyclin-dependent kinase inhibitors: identification by affinity chromatography using immobilised inhibitors. Knockaert, M.; Gray, N.; Damiens, E.; Chang, Y-T.; Grellier, P.; Grant, K.; Fergusson, D.; Mottram, J.; Soete, M.; Dubremetz, J-F.; Le Roch, K.; Doerig, C.; Schultz, P. G.; Meijer, L. (Station Biologique de Roscoff, CNRS, Roscoff, 29682, Fr.). Chem. Biol., 7(6), 411-422 (English) 2000. CODEN: CBOLE2. ISSN: 1074-5521. Publisher: Elsevier Science Ltd..

AB Background: Chem. inhibitors of cyclin-dependent kinases (CDKs) have great therapeutic potential against various proliferative and neurodegenerative disorders. Olomoucine, a 2,6,9-trisubstituted purine, has been optimized for activity against CDK1/cyclin B by combinatorial and medicinal chem. efforts to yield the purvalanol inhibitors. Although many studies support the action of purvalanols against CDKs, the actual intracellular targets of 2,6,9-trisubstituted purines remain unverified. Results: To address this issue, purvalanol B (I) and an N6-methylated, CDK-inactive deriv. were immobilized on an agarose matrix. Exts. from a diverse collection of cell types and organisms were screened for proteins binding purvalanol B. In addn. to validating CDKs as intracellular targets, a variety of unexpected protein kinases were recovered from the I matrix. Casein kinase 1 (CK1) was identified as a principal I matrix binding protein in Plasmodium falciparum, Leishmania mexicana, Toxoplasma gondii and trypanosoma cruzi. Purvalanol compds. also inhibit the proliferation of these parasites, suggesting that CK1 is a valuable target for further screening with 2,6,9-trisubstituted purine libraries. Conclusions: That a simple batchwise affinity chromatog. approach using two purine derivs. facilitated isolation of a small set of highly purified kinases suggests that this could be a general method for identifying intracellular targets relevant to a particular class of ligands. This method allows a close correlation to be established between the pattern of proteins bound to a small family of related compds. and the pattern of cellular responses to these compds.

REFERENCE 5: 131:228582 Synthesis and application of functionally diverse 2,6,9-trisubstituted purine libraries as CDK inhibitors. Chang, Young-Tae; Gray, Nathanael S.; Rosania, Gustavo R.; Sutherlin, Daniel P.; Kwon, Soojin; Norman, Thea C.; Sarohia, Radhika; Leost, Maryse; Meijer, Laurent; Schultz, Peter G. (Lawrence Berkeley National Laboratory and the Howard Hughes Medical Institute, Department of Chemistry, University of California, Berkeley, CA, 94720, USA). Chem. Biol., 6(6), 361-375

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(English) 1999. CODEN: CBOLE2. ISSN: 1074-5521. Publisher: Current Biology Publications.

AB Purines constitute a structural class of protein ligands involved in mediating an astonishing array of metabolic processes and signal pathways in all living organisms. Synthesis of purine derivs. targeting specific purine-binding proteins in vivo could lead to versatile lead compds. for use as biol. probes or drug candidates. We synthesized several libraries of 2,6,9-trisubstituted purines using both soln.- and solid-phase chem., and screened the compds. for inhibition of cyclin-dependent kinase (CDK) activity and human leukemic cell growth. Lead compds. were optimized by iterative synthesis based on structure-activity relationships (SARs), as well as anal. of several CDK-inhibitor cocrystal structures, to afford several interesting compds. including one of the most potent CDK inhibitors known to date. Unexpectedly, some compds. with similar CDK inhibitory activity arrested cellular proliferation at distinctly different phases of the cell cycle, and another inhibitor directly induced apoptosis, bypassing cell-cycle arrest. Some of these compds. selectively inhibited growth of cells derived from specific tumors. 2,6,9-Trisubstitu ted purines have various and potent biol. activities, despite high concns. of competing endogenous purine ligands in living cells. Purine libraries constitute a versatile source of small mols. that affect distinct biochem. pathways mediating different cellular functions.

REFERENCE 6: 131:97125 A cyclin-dependent kinase inhibitor inducing cancer cell differentiation: biochemical identification using Xenopus egg extracts. Rosania, Gustavo R.; Merlie, John, Jr.; Gray, Nathanael; Chang, Young-Tae; Schultz, Peter G.; Heald, Rebecca (Department of Chemistry and Howard Hughes Medical Institute, University of California, Berkeley, CA, 94720, USA). Proc. Natl. Acad. Sci. U. S. A., 96(9), 4797-4802 (English) 1999. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

AB Cellular differentiation is a complex process involving growth arrest, exit from the cell cycle, and expression of differentiated cell-type-specific functions. To identify small mols. promoting this process, a chem. library was screened by using a myeloid leukemic cell line that retained the potential to differentiate in culture. In the presence of a purine deriv., aminopurvalanol (AP), cells acquired phenotypic characteristics of differentiated macrophages and became arrested in the cell cycle with a 4N DNA content. AP also inhibited mitosis in Xenopus egg exts., suggesting that it acted on an evolutionarily conserved cell cycle regulatory pathway. Affinity chromatog. and biochem. reconstitution expts. with Xenopus egg exts. identified cyclin-dependent kinase (CDK) 1-cyclin B as a target of the compd. Although AP potently inhibited immunoppts. of both human CDK1 and CDK2 from human leukemic cell exts., our results indicate that the compd. preferentially targets the G2/M-phase transition in vivo.

REFERENCE 7: 131:82944 Methods of using chemical libraries to search for new kinase inhibitors. Gray, Nathanael S.; Schultz, Peter; Wodicka, Lisa; Meijer, Laurent; Lockhart, David J. (The Regents of the University of California, USA; Affymetrix; Centre National de la Recherche Scientifique). PCT Int. Appl. WO 9934018 A1 19990708, 103 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US27405 19981223. PRIORITY: US 1997-68798 19971224.

AB The generation of selective inhibitors for specific protein kinases would provide new tools for analyzing signal transduction pathways and possibly

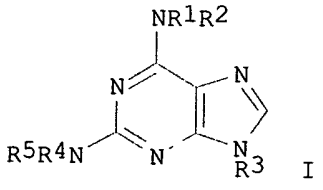
new therapeutic agents. We have invented an approach to the development of selective protein kinase inhibitors based on the unexpected binding mode of 2,6,9-trisubstituted purines to the ATP binding site of human CDK2. The most potent inhibitor, purvalanol B (IC50 = 6 nM), binds with a 30-fold greater affinity than the known CDK2 inhibitor, flavopiridol. The cellular effects of this class of compds. were examd. and compared to those of flavopiridol by monitoring changes in mRNA expression levels for all genes in treated cells of Saccharomyces cerevisiae using high-d. oligonucleotide probe arrays.

REFERENCE 8: 131:54006 Exploiting genomics in the search for new drugs. Lockhart, David J.; Wodicka, Lisa; Ho, Ming Hsui (Affymetrix, USA). PCT Int. Appl. WO 9932660 A1 19990701, 73 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US26925 19981218. PRIORITY: US 1997-68289 19971219.

AB The cellular effects of potentially therapeutic compds. are characterized in mammalian cells and yeast. In the latter case, the effects can be characterized on a genome-wide scale by monitoring changes in mRNA levels in treated cells with high-d. oligonucleotide probe arrays.

REFERENCE 9: 130:196532 Preparation of purine derivatives as inhibitor of protein kinases, G-proteins and polymerases. Gray, Nathanael S.; Schultz, Peter; Kim, Sung-Hou; Meijer, Laurent (The Regents of the University of California, USA). PCT Int. Appl. WO 9907705 A1 19990218, 67 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US16388 19980806. PRIORITY: US 1997-55400 19970807.

GI

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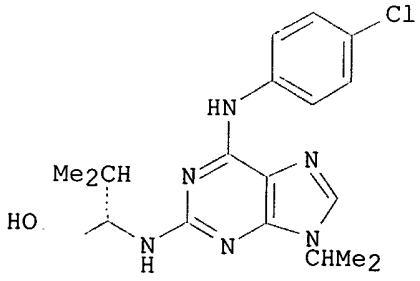


II

AB The purine analogs I (R1, R2, R3, R4, R5 are independently members selected from the group consisting of H, C1-C8 straight-chain, branched-chain, satd. and unsatd. alkyl, C1-C8 straight-chain, branched-chain, satd. and unsatd. substituted alkyl, aryl and substituted aryl) or a pharmaceutically acceptable salt thereof were prepd. for inhibition of inter alia, protein kinases, G-proteins and polymerases. In

addn., the present invention relates to methods of using such purine analogs to inhibit protein kinases, G-proteins, polymerases and other cellular processes and to treat cellular proliferative diseases. Thus, 2-fluoro-6-chloropurine was alkylated with 2-propanol followed by amination with 3-chloroaniline and then S-2-amino-3-methyl-1-butanol to give the purine II.

REFERENCE 10: 129:227384 Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors. Gray, Nathanael S.; Wodicka, Lisa; Thunnissen, Andy-Mark W. H.; Norman, Thea C.; Kwon, Soojin; Espinoza, F. Hernan; Morgan, David O.; Barnes, Georjana; LeClerc, Sophie; Meijer, Laurent; Kim, Sung-Hou; Lockhart, David J.; Schultz, Peter G. (Howard Hughes Med. Inst., Univ. California, Berkeley, CA, 94720, USA). Science (Washington, D. C.), 281(5376), 533-538 (English) 1998. CODEN: SCIEAS. ISSN: 0036-8075. Publisher: American Association for the Advancement of Science.

AB Selective protein kinase inhibitors were developed on the basis of the unexpected binding mode of 2,6,9-trisubstituted purines to the ATP-binding site of the human cyclin-dependent kinase 2 (CDK2). By iterating chem. library synthesis and biol. screening, potent inhibitors of the human CDK2-cyclin A kinase complex and of Saccharomyces cerevisiae Cdc28p were identified. The structural basis for the binding affinity and selectivity was detd. by anal. of a three-dimensional crystal structure of a CDK2-inhibitor complex. The cellular effects of these compds. were characterized in mammalian cells and yeast. In the latter case the effects were characterized on a genome-wide scale by monitoring changes in mRNA levels in treated cells with high-d. oligonucleotide probe arrays. Purine libraries could provide useful tools for analyzing a variety of signaling and regulatory pathways and may led to the development of new therapeutics.

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L7 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2002 ACS
1998:494641 Document No. 129:227384 Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors. Gray, Nathanael S.; Wodicka, Lisa; Thunnissen, Andy-Mark W. H.; Norman, Thea C.; Kwon, Soojin; Espinoza, F. Hernan; Morgan, David O.; Barnes, Georjana; LeClerc, Sophie; Meijer, Laurent; Kim, Sung-Hou; Lockhart, David J.; Schultz, Peter G. (Howard Hughes Med. Inst., Univ. California, Berkeley, CA, 94720, USA). Science (Washington, D. C.), 281(5376), 533-538 (English) 1998. CODEN: SCIEAS. ISSN: 0036-8075. Publisher: American Association for the Advancement of Science.
AB Selective protein kinase inhibitors were developed on the basis of the unexpected binding mode of 2,6,9-trisubstituted purines to the ATP-binding

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